

Fox, Philip C. 1998

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Dr. Philip Fox
Oral History Interview

April 6, 1998

This is an oral history interview with Dr. Philip Fox at the National Institutes of Health on April 6, 1998. This interview is being conducted by Dr. Ruth Harris and Dr. Victoria Harden in conjunction with the National Institute of Health Oral History AIDS Project and the History Project for the National Institute of Dental Research.

Harris: Dr. Fox, what led you into the field of dentistry?

Fox: Well, I have a father who's a dentist; so it was sort of the family business. But, in many ways it was the situation in the world about me as I finished college, which was in 1969. And at that time, of course, there was the Vietnam War going on around us. I wanted to do something in the sciences, and I also wanted to do something so I wouldn't get drafted. So with the combination of the two, dentistry was a good choice for me.

Harris: Did you undertake any dental science research at Columbia, which is your alma mater?

Fox: Yes, I did. I went to Columbia both as an undergraduate and then for dental school. And in dental school, I came under the influence of Irwin Mandel, who is sort of the dean of salivary researchers. Amongst those in the field, he is known as the "grandfather of spit," and he was a very important influence then, and still is, for me and for my research. I worked in his laboratory from the beginning of my second year in dental school. In fact, in my last year in dental school I was able to take part in a special program, an elective program that was offered, and I spent 80 percent of my time doing laboratory research with Dr. Mandel.

Harris: What was your laboratory research?

Fox: I was looking at some high molecular weight salivary proteins. Dr. Mandel was one of the founders of the field of sialochemistry, which was looking at the composition of different salivas and in different diseases. He was particularly interested in the role of these very large salivary molecules, and we were doing some initial work attempting to isolate some of these forms, with very little success, I might add, we were beginning to use some of the immunological techniques that were just coming into common use in laboratories then, things like radioimmunoassays and some of the immunoprecipitation kinds of assays that were just being used at that point. This was in 1972-73.

Harris: Your residency took place at the Harlem Hospital Center. Could you please describe briefly your work there?

Fox: My residency training was in oral and maxillofacial surgery, and I was at Harlem Hospital from 1973 to 1976. It was an exceedingly clinically oriented, trauma-oriented program, and I did almost totally clinical work as an oral surgeon. A lot of good, basic surgical training with very little opportunity to do much research. With the exception of maintaining some ties to Dr. Mandel's lab and sort of trying to finish up some of the things that I had left as a student, it really was a clinically oriented residency program.

Harris: What induced you to undertake clinical research?

Fox: Well, I think that that was actually a process that took place during my time here at NIH. When I first came to the NIH in 1976, I went into a purely laboratory-based program. I worked with Reuben Siraganian, and we were doing work primarily in immediate hypersensitivity and IgE-mediated immune responses, allergic responses, which is his work, and has been for many years. I did not see any patients. I just worked in the laboratory. I loved doing it. But after a number of years, I began to miss some of the interactions with patients, the part of translating some of the work that I was doing in the laboratory to people. I think that I went into research as opposed to staying in clinical care because I was very concerned about spending my entire professional life treating conditions that I didn't understand, that I might have great facility at managing but didn't really understand the nature of. I also would say that because of where I did my training, Harlem Hospital, which at that time was the second busiest emergency room in the United States, I also felt that being on sort of the end-product delivery of health care was a losing proposition. You would never catch up. At least that's the way I felt when I worked at Harlem Hospital. All you did was patch people up and put them back on the street, and it really seemed to me that not only was this a futile task, somehow we were not addressing the underlying causes that were bringing them into the emergency room either. Socially or even from a medical point of view, we weren't dealing with the underlying problems. I came to believe that I could have more impact if I understood the disease and could deal with it at that level rather than trying to fix it up after the fact. So that's what brought me into research. After about six and a half years of doing laboratory research, I felt that it was a wonderful luxury. I loved doing it, but I really wanted to have a little more contact with patients and also to try to combine the two.

Harris: Was the laboratory research with NIDR?

Fox: Yes. It was in one of the NIDR extramural laboratories. At that time it was called the Laboratory of Microbiology and Immunology. The chief of that lab was Steve Mergenhagen and Reuben Siraganian was my section chief, and I was a research associate. Interestingly enough, just parenthetically, I would add that I was one of the very few dentists at that time in the intramural program. There were really very few of us.

Harris: What brought you to the NIDR in the first place? How did you learn about it?

Fox: Irwin Mandel, my mentor. He, as I said, has been very influential in a number of places in my career. First of all, he influenced my going into oral surgery, which many people said seemed like a strange choice for someone who is interested in research. But I've always liked working in a hospital. And I enjoyed, I think, the technical aspects of the surgery and the management aspects of treating patients in a hospital setting. He was very encouraging of my doing that, saying, there weren't enough research-trained oral surgeons; so it would be a good field to go into. However, when I finished that training or was coming toward the end of finishing that training and had come to the recognition that I would not spend my career being a clinician, I said, "I don't really know what to do now." He knew the research I'd done in his lab and my interest in it. He knew the training I had, and he said to me, "Did you ever consider going to NIH?" I'd never heard of NIH, or I probably heard about it peripherally, but it never occurred to me that it was something that I might do. And he said, "Well, you ought to consider NIDR for a fellowship, do that, see what you think of that kind of work." He knew Steve Mergenhagen quite well and arranged an appointment for me to come down and talk to him. So I came down for that interview. I talked with Steve Mergenhagen, and it actually became clear that we had very little interests in common, but when we talked about what I had been doing and what I was interested in, he said, "You ought to talk to Reuben Siraganian, call him up." I came over and talked to Reuben, and he offered me a job. So I came down here in 1976 for two years.

Harris: You're still here.

Fox: And I'm still here, yes.

Harden: This is a common story.

Fox: Yes.

Harris: Now, you've given us some background on your salivary research. Can you give some background on your immunology research and tell us whether or not it started before or after you came to the NIDR.

Fox: Well, I think that to some extent it started before. When I was a student at Columbia, Dr. Mandel's lab was doing a lot of work with secretory IgA. That was one of the molecules that he studied. As a student at Columbia, we had some excellent instructors in immunology, which was a very new field then in many ways. For example, Elvin Kabat taught at the medical school, and the dental students took their basic science courses in with the medical students, in a conjoint program. So we had this excellent training in basic immunology, which seemed like a fascinating area. And actually, as a student, working with one of the younger faculty members, I went through a programmed instructional course in clinical immunology. And then, of course, when I came down here, the work that Reuben Siraganian's lab was doing was all in immunology. We got involved very early on in the production of monoclonal antibodies. Just the production of them, in fact, was something of a technical achievement worthy of publications unto itself, and we got involved in that. And, actually, some of my first publications in immunology were looking at methods of enhancing the yield of antigen-specific hybridomas. They were called hybridomas then, not monoclonal antibodies. It's interesting how serendipity always plays such a big role, I think, in what you end up doing. My lab at that time was next door to Tom Chused's. And he had working in his lab, as a visiting fellow, Harry Moutsopoulos. Now, Harry Moutsopoulos, who is a Greek researcher, had been at the NIH for many years and is one of the leading researchers in Sjögren's syndrome. And because I was next door to them, and Irwin Mandel's lab had done some work on Sjögren's syndrome as well, I was familiar with it and I sort of kept track of what they were doing. I got to know the people in the lab next door and what some of their work was. A number of years later, when it came time for me to start my own project, Sjögren's syndrome seemed the perfect merging of my two interests, which were immunology and salivary gland research. Well, here's an immunologically mediated salivary gland disease, and that's how I came to work in Sjögren's. Also, NIH had a long history of research in Sjögren's with investigators like Joe Bunim and Norman Talal. Around this place, in the Clinical Center I remember the lineage of Sjögren's. The people who were studying it in the '70s were actually Tony Fauci's group, particularly, Cliff Lane—I still see some patients that he used to follow. The work that they were doing in Sjögren's, in vasculitis, in management of these immunologically mediated conditions, was very exciting. Really important work was being done, and it was an exciting time to be here.

Harden: May I jump in and say, I'm trying to, have been trying to put together how the intellectual picture emerged when AIDS appeared in '81, and so the '70s have really interested me. And do you have comments or memories of this flowering of immunology, of the excitement of every week it was something new practically. And the monoclonal antibodies were definitely the hot thing at the end of the '70s. If you have any further expansion on that, I'd be glad to hear it.

Fox: Yes, it was very exciting. Actually, I've often said I think one of the reasons that I loved immunology so much is that when you were talking about a classic paper, it was one that was eight to 10 years old, as opposed to, if you were in cardiology, to one from 120 years ago. It was very current. There were new things. There were the seminars. Someone would come and present something, and the next week you'd be working on it and incorporating it into your lab. It was a very exciting time to be here. A personal reminiscence, as an example, is the first presentation I ever gave at a scientific meeting. It was at a dental research meeting and it was here in Washington, D.C. The abstract that I had put in was on the creation of antigen-specific monoclonal antibodies. We had made the assumption that there would be minimal interest in it, at this meeting, because the dental research meetings are very broad. They're very large meetings and a lot of different disciplines are represented. We figured that this would appeal to a few people, but not to very many, and that was fine with me because I was pretty nervous, it being my initial presentation. And I happened to be the first paper in the afternoon session at one of these small oral sessions. When I got to the room to give the talk, you couldn't get in the room. It was jammed, just because the topic then was so relevant—certainly nothing about me, nobody knew who I was. But the topic was something that so many researchers recognized that this was something they could use, that the place was absolutely packed. And, of course, I was somewhat panicked by this, having to give my first talk. But it was a good start anyway.

Harris: In your salivary and immunology research, have you coordinated the work with the epidemiology and other intramural scientists involved in salivary research, both in NIDR and in other institutes?

Fox: Yes. I think that particularly with the work that we've done in Sjögren's and in the HIV-associated salivary gland disease, there's always been a lot of collaborations within the institute and also within the various institutes. By its nature these are conditions that cross over a lot of boundaries, and we've generally collaborated with people who had interest and expertise that were appropriate or similar to ours. So I think I probably collaborated with people from, I believe, half the institutes, I'm sure, and, as well as, of course, many, many people outside the NIH in general. It's interesting. Salivary research is not a huge field; so that over time you get to know most of the people who are involved in it, at least those who sort of stay in it, and you end up probably working with them one way or another, most of them, after a number of years.

Harris: Can you give a ballpark estimate of how many scientists are in the field of salivary research?

Fox: Well, that's hard to answer. I think that the salivary research group in the American Association of Dental Research has about 150 or 160 members, but obviously that doesn't represent everyone who does salivary research. So I suppose it's something more than that. But there probably are, I would imagine, no more than 200 or so that work really full time in the field.

Harris: Are most of the salivary researchers in the United States, or are they spread all over the world?

Fox: I think they're spread all over. Certainly there is, as with a lot of biomedical research, a solid core in the United States. But there are a lot of Scandinavian, European, and Japanese researchers. It's pretty international.

Harden: I want to jump in before you even get to your specific HIV research, and just ask you to think back as to when you first heard about AIDS as a new disease and what context you heard it in and how you began to think about it.

Fox: Well, I certainly can remember the first paper in the *New England Journal of Medicine* pretty well. I remember, actually, very early on—I'm not sure what year, but I would say maybe even in '82—a clinical staff conference or grand rounds that was held. At that conference they were discussing AIDS before it had a name, whatever it was being called at that point, perhaps GRID. They were discussing those first cases that were being reported out of San Francisco, and I can remember Tony Fauci giving a grand rounds, talking about this condition very early on. That was probably the first that I was aware of it, and it was certainly well before it was being widely talked about.

Harden: Or defined as a virus.

Fox: It had not been defined.

Harden: Caused by?

Fox: Cause had not been defined at that point. That I remember.

Harden: Did you have any sense that you might end up working on it at that point in time in your career?

Fox: No, not really. It seemed like a fascinating condition because of the acquired immunodeficiency, but I didn't see the connections at that point, particularly because then was when I was just beginning to move over into and establish my own clinical research program, which was looking at salivary gland disease and dry mouth and various causes associated with it. So it just was a matter of interest as something of an immunological nature and for someone interested in clinical immunology.

Harris: What led you to investigate the HIV and its effects on human salivary disease?

Fox: I think there are a couple of reasons. The first is that, from quite early on, as the larger reports of HIV disease began to come in, the oral cavity was involved. In fact, one of the very early papers described oral candidiasis as being an important marker for disease progression. So from very early, it was clear that there were specific manifestations in the oral cavity that were important and common in this disorder. So since my bias is that saliva is important for anything that happens in the mouth, it seemed to me that there was a potential connection there, in particular because there is such a very clear association between salivary gland dysfunction and oral candidiasis. In other words, in the condition I study, in Sjögren's, where you have diminished salivation, one of the problems that you commonly have is recurrent oral candidiasis, and that is related to the loss of the protective antifungal factors, among other things, that are in saliva. So, number one, there was the clear connection to the oral cavity, and in particular, to an oral manifestation that is commonly associated with salivary gland dysfunction. This led us to our studies looking at salivary alterations and the saliva itself and salivary function in HIV disease. The second reason, which is what really led us to the specific studies that we did in terms of anti-HIV activity in saliva was the fact that, as the epidemiology began to become a little more clear in this disorder, it also seemed to be clear that HIV was not being transmitted by an oral route. And that's very interesting because, clearly, there was transmission by other mucosal routes, anal or vaginal, yet not by the oral cavity. Yet the mucosas are quit similar. So we asked the question, what's different? Saliva is different. In the mouth you have saliva. Now, clearly that may be simplistic and that may not be the only answer, but it's what led us to look to see if there was something special about saliva that was helping protect the oral cavity.

Harden: All right. Let me follow up on that, too. To shift one bit, I know there are also lymph nodes in the gut which may be anal routes, so apparently made transmission so easy. You've got lymph nodes here in your neck, but the saliva was able to protect against that in a way that it wasn't in the gut.

Fox: You have to realize that, first of all, I don't think we still know the answer exactly. But what we were looking at is, I think, a striking difference in the transmission risk. We considered other factors, and there are a number of other factors other than saliva. But the most striking, at least to us, since we study salivary function, was to look at the saliva, and that's how that came about.

Harden: I've got a couple more things in this particular thing I wanted to ask you. One has to do with the transmission from patients to dentists, or the one exception to that rule where the dentist infected the patient. Did you get much epidemiological data along those lines as feeding into your thinking on this? I know the Dental Institute very early on put out some guidelines for practicing dentists, and I didn't know how much you in the laboratory were involved with any of that kind of work, of public outreach, and having that come in and feed your thinking.

Fox: Well, I think most of the way that we were involved in public outreach was that every time some story would appear that had any bearing on the oral cavity, I'd get a call about it, and that was the main thing. It was more in terms of reaction. In general, what we did was we were monitoring the epidemiological data and following it closely because it clearly was providing some backing for our thinking that there was something protective in saliva. And it's very interesting that actually dentists have very low risk, and this was even at the time when dentists were not routinely wearing gloves. There was virtually no transmission from patient to dentist. There were some initial reports that virus could be found in saliva. So, again, why was it that dentists weren't being infected? Why was it that it wasn't going the other way, that there was less transmission? The evidence seemed to support the contention that there were very few dentists who were both infected and practicing. Still, with the exception of one still unexplained case, there was no evidence for transmission. And so, again, everything just seemed to be pointing to there being some unique factors in the mouth that were helping.

Harden: There has been a case recently, in the last year or so, about transmission by kissing, and my understanding—maybe you can tell me here—is that both the people involved had serious gum disease, and apparently the saliva simply couldn't overcome this massive ability of the virus to reach the blood. Do you want to talk about that?

Fox: I don't really know all the details of the case, and there have been a number of these. I would say that in virtually all of the cases I'm aware of, there is very little proof of the route of transmission. That's number one. But the argument that I make is that even if we accept every proposed case where there was oral transmission, be it through a fight or be it through kissing, it adds up to seven or nine cases, something like that, that have been put in the literature. Let's say it amounted to 20. The pertinent question is what's the denominator? Oral transmission appears to be such a vanishingly small percentage of the cases that it's not a risk that should give one, certainly from a public health point of view, very much concern. And it always interests me, in fact, that there is such a hue and cry every time one of these cases comes up, which I think, just personally, is more a reflection of the public's difficulty with this whole topic and with trying to change behavior. People don't like to go to the dentist very often, and so it's very easy to get very concerned about, "Oh, am I going to get infected at the dentist's office?" as opposed to dealing with what are the real and well-documented risk factors and risk behaviors which people have a lot harder time talking about.

Harden: Yes. It's a lot easier to explain to your spouse that you caught it in the dentist's.

Fox: Right. Exactly right.

Harris: The Clinical Center accepted AIDS patients by the summer of, I believe, 1981, and the dental clinic did treat some of these people. Did the dentists who worked with the AIDS patients wear gloves and face masks and protective garb when they worked with the AIDS patients here?

Fox: They did certainly use gloves. I can't speak specifically to face masks, but certainly gloves were universal in the clinic from the 70s. This was something that was done 100 percent of the time. I should explain that we sought not just the protection of the dentist and the patient individually, but also, since we deal so frequently with medically compromised patients, there's a protection of the patient from any potential transmission from the clinic or procedure. So I think that we were definitely well ahead of the curve in terms of use of gloves and then masks. As the various different regimens were suggested, we were generally either already doing them or certainly had instituted them. So infection control practices were, I think, being done here probably before they were being widely used in the outside, in the general practice.

Harris: Now, in your investigation of the AIDS virus, did you work with animals here at all?

Fox: No, I didn't. We did cell culture work, and then our clinical, our human studies, but we didn't do any animal work, not with HIV.

Harris: The saliva that you used to study, did it come from the AIDS patients who were in the Clinical Center?

Fox: Yes. The AIDS patients that we studied were all Clinical Center patients. We looked at both patients and also we looked at healthy controls.

Harris: Do you recall when you started studying the saliva of the AIDS patients?

Fox: I'm not exactly sure what year it was. I know that it probably was, I would guess, in probably '84, '85 that we studied this.

Harden: This paper was '88.

Fox: But we were actually looking at some of the salivary alterations in HIV infection earlier than that, looking at changes in the gland and the saliva. Essentially, once it was clear that this was a condition with many oral manifestations, we then began to study it.

Harden: And that there was a virus defined?

Fox: Yes.

Harden: Okay.

Harris: In other words, you started the research Did you start looking at the saliva after it was defined as a virus, or before?

Harden: I think it probably was after. Probably it had already been defined as a virally induced condition when we started to look at the salivary changes. And it was interesting because there were so many reports that were coming out, and they were often, if not conflicting, then difficult to sort out because people were employing a lot of different techniques and definitions. For example, I remember one report that came out, which was correct but was a little confusing, that scientists were reporting that they were recovering a lot of CMV from the saliva of HIV and AIDS patients. And then, so the question was, was somehow this related to CMV infection? Did it reactivate CMV infection? Was it a co-infection? There were all sorts of theories that came around. But I think it probably was after the time at which we knew that it was a virus that was causing the condition.

Harris: You have done a lot of work on dry mouth.

Fox: Yes.

Harris: Did the dry-mouth research, a lot of which you did in the 1970s, lead into the AIDS research? Did it have any influence on your AIDS research?

Fox: I think it was a natural extension in that we were a group that studied salivary gland function and dysfunction, and here was a condition that looked like it had manifestations that could be associated with salivary dysfunction. And what we initially started out to do in a very simplistic way was just to try to identify whether there were consistent and recognizable changes in the salivary function or in some of the salivary constituents that might be associated with this condition, and which then might also relate to the clinical findings. So, yes, it was a natural extension. And, as I said, the work that we did in terms of looking at what are the functions of saliva and how it functions in the oral cavity; for example, studies of antifungal properties, antimicrobial properties, and some antiviral properties that had been described previously clearly are what led us to look for anti-HIV activity.

Harris: Can you please tell us how your team came to look into the antiviral antibodies in saliva?

Fox: It wasn't really antiviral antibodies. Antiviral antibodies had been described previously, but they were not neutralizing. That had been seen. We were actually looking for something other than an antibody. We were open to any kind of antiviral constituent or activity that we could find. I should actually tell you a little bit about the story, because I rather enjoy it myself. We had this idea, as I said, that what was different about this mucosal surface, the oral cavity, was that there was saliva present, and so we thought to ourselves, there must be something in saliva that has antiviral activity. And we thought this was a terrific idea, and we started to plan a whole series of experiments. None of us had seen anything like this. But we figured, you always want to start by checking the literature. And guess what? Somebody had already thought of it and actually had published it. There was a paper. Actually, it was a letter to *Lancet* by a woman named Patricia Fultz, who at that time was at the CDC, and she had published a letter in *Lancet* saying that there was salivary HIV inhibitory activity, and we were totally amazed. Somebody had done this experiment as far as we could see. Well, we then looked at the published letter in more detail. It was short, first of all, but also it turned out that it wasn't quite so clear-cut for somebody who studies salivary glands. What she had done was the following. She was working with chimpanzees and was looking at issues of transmission. What they would do is that they would swab the vaginal mucosa with high infectious doses of SIV, and they would invariably get seroconversion. The animals would become infected. And they tried doing it in the oral cavity, figuring mucosa is mucosa. So they swabbed the oral cavity, and the monkeys weren't getting infected. And so she thought, much as we did, gee, what's different? Must be something about the saliva. So she collected saliva from these, I think they were chimps, and co-cultured it with virus, and showed that you could inhibit the ability of that virus to infect white blood cells. And then she did the same thing with her lab technician. She had the lab technician spit into a tube, took that saliva, which I would not call saliva, I would call spit. This is where we get into the fine distinctions. And she did the test and found out that here was a human sample that was able to inhibit the infectivity of the virus. This was exactly what we had in mind. The only thing is that she had used what one would call whole saliva; that is, she took this expectorated fluid content of the mouth. Now, if you study salivary glands, what you know is that the whole saliva has serum in it and serum products and bacteria and bacterial products and a lot of proteases. It has all kinds of things in addition to the secretions of the salivary glands. So when we looked at it, we said, "Well, she was thinking the same way we were, but the problem is she didn't actually get saliva;" that is, a pure secretion from the salivary glands. It could well have been something that was in the serum or was in the mouth, although it likely was from the saliva, but it wasn't really clear. And so our first work really replicated those experiments that she did, except that what we looked at was pure saliva; that is, we took a secretion individually from the parotid glands or from the submandibular/ sublingual glands. We looked at the secretions effects first by culturing with the virus and then trying to infect in a cell culture system. We were able to show that the inhibitory activity in fact was something that was coming from the salivary glands. It did not appear to be an antibody, per se. We, however, never specifically identified what that antiviral factor was.

Harris: What do you know about this situation today?

Fox: Well, subsequently, people have identified a couple of different factors in saliva that seem to play a role. And probably the most specific work that has been done, which really followed on what we did, is the work that Sharon Wahl has done with SLPI. She was able to show that at physiologic concentrations of the secretory leukocyte protease inhibitor, which is found in saliva, they were able to get essentially those same effects of very profound inhibitory effect on HIV infectivity. Other investigators have shown inhibitory activity from other salivary components. At the time that we published that first paper there was a tremendous amount of interest. It was definitely our 15 minutes of fame, with phone calls from all over the world, actually. And I think that the reason that it really attracted so much interest was that it was a positive, hopeful finding. Rather than something that was frightening, it actually was reassuring to people that here was something that was natural, that there was some defense that everybody had because we showed that it was in both healthy individuals and in people who had HIV infection. All of them seemed to have this factor, whatever it may have been, that was quite potent and capable of inhibiting infectivity. And so I think it appealed to people in that sense, which is why it was so widely disseminated.

Harris: Then you would say that the date that this particular piece of research started followed the letter that you read by Patricia Fultz?

Fox: Oh, yes, by a good two years. I mean, it actually amazed me that for whatever reason her report just did not get picked up. People did not appreciate the significance of it. I never saw it referenced anywhere until we referenced it in our paper. Certainly the significance was overlooked, and, additionally, from her perspective, I think it was a sideline to what her major research interests were. So she moved on to other things, and there was no reason to pursue it.

Harden: Would you mind clarifying for me where all those other factors in spit come from that aren't saliva?

Fox: Well, serum and serum factors come from the gingival crevicular fluid, which is actually a serum ultra-filtrate that comes up in the crevice that's around every tooth. There's a little collar formed by the gingiva, and from the base of that comes this ultra-filtrate of serum. Additionally, if there are any breaks in the mucosa, there is movement of serum and serum products through into the oral cavity. Obviously, bacteria grow all the time. You can even find some bronchial secretions which are coming from the lung. So there's a lot of other stuff that's there. Many, many proteins are produced in the salivary glands and are secreted into the oral cavity, families of proteins.

Harden: Are they different in different people, or is this a common genetic factor?

Fox: Well, there are certainly polymorphisms. They're not absolutely the same. But in general, people have pretty much the same complement of families of proteins in the secretions.

Harris: You mentioned Sharon Wahl's work on SLPI. Did you have any direct connection with Sharon Wahl before your article was published? Did she know about your work? Did that influence her to look into this matter?

Fox: First of all, Sharon and I used to be in the same lab, in Steve Mergenhagen's lab for many years; so I've known her for a long time. She probably didn't specifically know about the work that we were doing till we published it, and then, of course, everyone in the Institute knew. We then spent quite a bit of time replicating and being certain that the finding was correct. I think that there was within the Institute a fair amount of questioning of the experimental findings, more so than there was in the outside community. But within the Institute there was a lot of questioning. Could this be absolutely certain? And, in fact, a couple of years after the initial report, Sharon was responsible for supervising a postdoc who did some of the work that was reported in the third paper in that series. That was Dr. Chih-Ko Yeh. He actually worked with Sharon in her laboratory to do some more of the work and to extend some of the findings. I think that it was based on that interaction that led her to continue looking at some other factors. Now, she had been doing AIDS and AIDS-related research in different topics. I mean, she's been very interested, as you know, in monocytes and the role of monocytes in HIV infection and alterations in monocyte function for a long time. This was sort of the connection between her work and the work that we had been doing. And at that point we had pretty much stopped doing any antiviral work, and so she sort of took over that part of it. And then I guess the finding with the SLPI came out of other research that she was doing with a company that had the purified protein.

Harden: One little tiny note. You were talking about the reviews, that the criticism in-house, is it really true. What you're describing, I presume, is simply the rigorous in-house peer review that everybody goes through here rather than anybody's just blind assertion that, well, it can't be or whatever. You're talking about presenting your papers, your ideas, and having your peers criticize it. Correct?

Fox: Right. In particular, our scientific director at that time was a virologist.

Harden: Dr. Notkins?

Fox: Yes. And so I think he had a particular interest in this, and for the interaction, and he was highly skeptical of the finding. We had many long and heated discussions about it, and he was certainly instrumental in seeing that the Institute would do a series of continuing experiments to initially replicate and then eventually extend some of our findings.

Harden: By the time you published it, you felt very confident.

Fox: I never had any lack of confidence.

Harden: We've talked about this with a lot of different people.

Fox: Certainly, I think that the initial paper was published quickly. By the time the subsequent papers came out, there was really no doubt as to the validity of our observations.

Harden: There was no question anybody could raise that you couldn't answer. That's the way I should phrase it.

Fox: I would agree with that restatement.

Harris: In one of your articles, you noted that Kaposi's sarcoma in salivary glands usually is very rare. Does that hold true for patients infected with HIV?

Fox: Yes, I believe, at least in terms of in the salivary glands. I think that it is quite rare. I mean, there are very few cases that I'm aware of. But we haven't really studied that in detail, so I would be hesitant to state that with great certainty.

Harden: Let me just throw this in. I was reading in the clips today that they're asserting that it's the human Herpes virus 8 that I think came out of Gallo's lab that may be the cause; they're arguing now, for this. And does saliva have an effect on herpes viruses, an inhibitory effect?

Fox: Generally not. Now, I don't know about HHV-8, but certainly the herpes viruses are very efficiently carried and transmitted by saliva. Herpes simplex is very common.

Harden: Yes, of course.

Fox: And there have been many reports on HHV-6 in saliva, and it's active and not inhibited. So, in general, the herpes viruses have not been found to be inhibited by saliva. And, again, as I said, saliva is a pretty efficient medium for transport for a number of viruses, which, was why we were so intrigued that that did not seem to be the case with HIV.

Harris: Have you found any drugs that treat successfully the oral manifestations of HIV?

Fox: We personally have not really been involved in drug development in this area. We've worked in development of a drug to treat dry mouth in the sense of stimulating salivary gland secretion, but we have not actually been involved very much in drugs for oral manifestations of HIV. We have worked in our dental clinic with some of the other institutes in looking at the effects of some of the newer antifungals on oral candidiasis, and we've just been involved in helping them do some of the clinical aspects of that. But that hasn't been a major aspect of my program.

Harris: Have you participated in any workshops on AIDS and the oral cavity?

Fox: Oh, yes. There have been a couple of workshops that were organized by John and Deborah Greenspan, and I've taken part in, I guess, both of those. And there have been a number of other ones through the years that I've taken part in, such as those dealing with some of the salivary alterations that one sees in HIV infection, and then dealing with salivary antiviral activities. That's been our main area. We've also done some collaborative work with the people at UCSF. We have specifically looked at this condition they call HIV salivary gland disease, which is typically where the patients develop enlargement of the glands, but often secretory dysfunction of a more pronounced nature than you see commonly in HIV-infection. And, in fact, it's been reported that the salivary glands actually develop histopathological changes that look something like Sjögren's syndrome, which is the condition that I study. Interestingly enough, there was a great deal of excitement when that was first reported, because people said, "Wow, we've been looking for a viral connection with Sjögren's for years," and so here we have it-not that HIV causes Sjögren's, but that clearly a virus could do that. What's interesting is that, subsequently, in work that others have done and that we've done in collaboration with the people at UCSF, we've been able to show that there are some significant differences between what you see in Sjögren's and what you see in HIV salivary gland disease. And although they may look somewhat similar at a light microscopic level there also are fairly consistent differences in terms of some of the things you see in the saliva, and certainly if you look at subset analyses of the cells that actually infiltrate the gland, there is quite a difference between those two conditions.

Harris: The Greenspans, are they at the University of California-San Francisco?

Fox: Yes, they are.

Harris: The Dental School or the Medical School?

Fox: At the Dental School, although, I believe that John Greenspan has a dual appointment, and Deborah Greenspan may as well. They're based in the Dental School.

Harris: I gather that they are supported by the extramural part of NIDR?

Fox: Yes, they are.

Harris: So this is where you cooperate with the extramural part.

Fox: Oh, yes. And they've really been leaders from the very beginning in looking at oral manifestations of HIV and defining a number of the really important lesions and the causes of them. Most of the initial work on hairy leukoplakia came from their group. And they've done a tremendous amount of work and have collaborated with a lot of people, including a number of people here in the intramural program. And I've worked with them on this project as well as others but also have collaborated with other people in the extramural community.

Harris: Have you done much on hairy leukoplakia?

Fox: No, I haven't.

Harris: Have you served on any groups involved with AIDS research, such as task forces or interest groups?

Fox: I guess I have been on some task forces here at the NIH that have looked at some of the plans for research, workshops involved in discussion and committees, for example, looking at the women and AIDS studies and others. So, yes, I've been on a few of those. I'm on a lot of workshops and committees. But that's generally been on an ad hoc basis.

Harris: How do you think your findings on the effects of saliva on HIV, and vice versa, can be used in the war on AIDS?

Fox: Well, I think that the findings of salivary constituents, or maybe I should just say components that may be found in saliva, and their antiviral effects could be very important. Obviously, some of the work that's coming out of Sharon Wahl's lab with SLPI and possibly some of the other factors that other people have been looking at, these may be important in looking at ways of preventing or lessening infection. I think that what we've seen in terms of the effects of the virus on the glands can also be useful in telling us something about what are the different factors that may alter salivary function and salivary histopathology. For example, while clearly there's a difference between Sjögren's and HIV salivary gland disease, it still shows that a virus can cause quite profound changes in the gland, and that's useful for us in looking at some of the other conditions that we study and potentially ways of interfering with those changes.

Harris: What do you consider your most important findings in your studies on HIV and the oral cavity?

Fox: I think it's the finding of the antiviral activity, that it actually comes from the salivary secretions and that this is capable of quite potent inhibitory activity in terms of HIV infection. And while I think that it's not proven, there's a fairly obvious connection between that observation and what is observed epidemiologically. First of all, it's been shown that saliva only rarely contains infectious virus, that when it does, it's in very low amounts and that, additionally, whatever number of cases there may be, there are very, very few times that saliva appears to serve as a route of transmission. And so I think that the way that our findings support and help explain those findings are unquestionably the most significant aspects of this work.

Harris: What scientific tools and advances in science do you think helped you the most in doing this research and doing any of your research on saliva?

Fox: Well, that's a good question. The late '80s and the '90s have been the era of molecular biology, and the tools of molecular biology have totally changed the way we all do research. As an example, we went from having to culture and actually try to titrate virus and counting syncytia and all sorts of fairly laborious things to being able to look at P-24 as a surrogate marker of viral RNA because those molecular tools became available and became more widely used. That greatly eased just how laborious some of the research was. And, subsequently, in the work that I've been doing in salivary glands, we've gone to using techniques that have allowed us to make findings that we just couldn't have made three years ago.

Harden: And these are mostly throwaway tools, I take it. These are not big instruments

Fox: Most of these are reagents although you have to buy a thermal cycler if you're going to do RT-PCRs. But, on the other hand, that has become as common a tool in most labs as a spectrophotometer.

Harris: What is a thermal cycler?

Fox: That's the instrument that is used when you do PCR, which is where you have to heat and cool very rapidly, in a cyclical fashion. It's the machine that does that.

Harris: We don't have one in the collection.

Fox: Well, you should.

Harris: Let's see if we can get one.

Fox: Because when Carrie Mullins first described PCR, it only works if you have a machine that can rapidly cycle through these different temperatures and bring your materials, your DNA, to set temperatures and then quickly lower them or raise them to separate and then re-anneal and do the different techniques.

Harden: Well, this is one of the things I was going to ask, too. If there are particular instruments, if you can either keep your eye out for them, if someone's going to get a new model, and I have a good example of something like this because this is the late '80s. So we would like to have this kind of thing. We have an Elisa—not an Elisa, a fax machine.

Fox: You should get a plate reader; you should get a first-generation plate reader also for Elisas.

Harden: We do have Elisas, but they're much older.

Fox: I guarantee if you go to surplus, I bet you'll find an old, early-model thermal cycler, because the ones now are all much improved.

Harden: Are there any special instruments that you use; have you, for this research, such as something to collect the saliva with?

Fox: Yes. I was going to say, the one thing that probably is a little different that we have that other people around wouldn't is that we have these collectors that we use. Now, they're not new. The first description I have of the one we use for collecting parotid saliva is from 1910. But these are little plastic collectors that we hook up to some tubing, and they hold on the inside of the cheek, and they cover the orifice of the parotid duct and allow us to get a pure secretion, which isn't something that everyone has.

Harden: If we send a form over here, could you help us get hold of one?

Fox: Sure.

Harden: You'll hear from me.

Harris: Are you still conducting clinical research on AIDS and the oral cavity?

Fox: No, we're not, not really. Our work now is almost solely in the area of autoimmune-mediated salivary gland disease or radiation-induced salivary gland disease. Those are really the two main areas that we study now. And we haven't done really very much with AIDS-related research in years.

Harden: What made you shift?

Fox: Well, actually, what I would say is that in some ways the AIDS work was really kind of a detour on our path, and it was a very fascinating and a necessary one to take. But, really, our work has always been with salivary gland disease and, in particular, my own interest in immunologically mediated salivary gland disease. It was only because we were doing that when AIDS arose, and it was such a huge public health problem as well as just such a huge scientific question that we then took what we were doing and said, let's look at what is the role here: what's happening in the salivary glands in HIV infection, and then what's the role of saliva on the infection? But, really, that was never the main thrust of our lab. The main thrust of what I had always been doing was in terms of looking at salivary dysfunction. I should add that after our initial observations that we made in terms of the antiviral activities, the Institute put out a specific request for protocols to the extramural community because they wanted to see this get worked on and funded elsewhere besides just here. And so we could see that at one point there were five different groups that had been funded to continue that work. There was some work that was continuing in the intramural program, and at that point we turned our attentions back to what had been the main thrust of the research, which was in Sjögren's and then some of the radiation work.

Harden: I need to follow up on this and ask you, because, of course, there had been a lot of criticism of the NIH early on that people didn't just drop everything and start working on AIDS. And one of the things that we hope to do is to try to show how people make decisions about what scientific opportunities present themselves. Would you comment just a little more? Was it the fact that AIDS was there and offered an opportunity, or did you have any push from above? Was there any incentive to divert into AIDS, or was it clearly a scientific opportunity? I mean, was it all mixed up?

Fox: I think it's a combination. Honestly, I think it's a combination of all of those. Certainly no one said, "Do something on AIDS." On the other hand, clearly, there was felt to be from Congress and from the public a tremendous pressure to be doing something and to be seen as responding to what was seen as this huge public health threat. And so, in that sense, there was a pressure. There was an imperative to do that. Obviously, also, there was funding available. It was being made available, and so it was attractive in that regard. So I think there were lots of reasons. It also presented, as I said, from our perspective, some very interesting questions that we might be able to answer from what we were doing and exactly what we had been asking: What causes, what controls oral candidiasis, candidal carriage in the oral cavity? What are some of the things that can cause salivary dysfunction? So all of it was there. Clearly, there were any number of reasons to pursue that path. Pressure was, to some extent, one of them. I think just, in general, this feeling that really everybody should be doing his/her part to do something and to try to find some answers here because people were alarmed. I think sometimes people forget how hysterical the public was. I, for example, remember really clearly reading newspaper stories about HIV-infected children who were not being allowed in kindergartens. And why? Look at the reasons they were giving.

Harris: Like biting.

Fox: Right. It was because of the oral cavity. It was all body fluid, but really they were talking about spitting on people and biting. Those were the two things, even though there was no epidemiology supporting that as a route. But kids were being discriminated against and people were being hurt. And so, from my perspective, that was an incentive to try to say, "Hey, wait a minute." I was quoted in the *Washington Post* after our salivary antiviral study was published as saying, "Saliva is your friend." And this came out of that initial report when I was being interviewed by one of the reporters. She was actually a friend of somebody that I work with here; so we were talking quite informally. And in the course of our conversation, we were talking about what this might mean to people. And I made the comment, that basically, our research is saying that as far as HIV goes, saliva is your friend. And, in fact, that was the sidebar in the *Washington Post* story, "Saliva is your friend," which we've adopted as our motto and have up in the lab.

Harden: Did you have any personal experiences with people in your neighborhood or other people who knew you were working on HIV and saliva, who wouldn't shake hands with you, who didn't want to be around you? We've asked this of a lot of people, too.

Fox: No. I wouldn't say that was really my personal experience. But certainly what I got a lot was from people who knew I worked at NIH and would say to me, "Do you do any work with those people?" And I would always say, "Yes, we see AIDS patients every day in the clinic." And at least the impression I got was that they didn't run out of the room. But people really were looking to people like me and other people who worked at NIH to give them some guidance. They really wanted to hear something like, "Oh, so you're okay about this?" I'd say, "Yes." I remember saying, "You're not going to catch AIDS shaking hands with somebody. You're not even going to catch AIDS kissing them. Now, what happens after you kiss them, that's a different story and that's where you may be in trouble." And I think that people heard that. But it's interesting. My experience was, I don't ever remember another patient coming into the clinic, for example, and saying, "Do you treat AIDS patients here?" Maybe that's just the nature of the Clinical Center, that's the way things are. It was not that direct, but, clearly, people were concerned and were certainly interested and were looking for something.

Harris: Does the fact that you did this AIDS research here have something to do with the overall policy and atmosphere at the NIH which, as I understand it, allows scientists a certain latitude to do the research that they want to do? Can you comment on that?

Fox: Well, I think certainly it's true that one of the great things about working here is that you have a lot of freedom, as long as you're doing good and productive work, to pursue areas of interest and opportunity, and clearly this fell under that. I'm not a virologist. I never claimed to be. I wasn't an AIDS specialist. But when we found something that was interesting, we at least were able to initially pursue it. There was a lot of discussion after those initial papers as to what we would do in the intramural program about this, and, actually, there was probably some decision that I had to make at that point as to how much I wished to pursue it. And I said very clearly at that point, "I'm not a virologist, my lab isn't a virology lab. Really, if we're going to pursue this, I think that it has to be done by someone who has more expertise specifically in the area." My expertise is in salivary glands and salivary activities, and that's how we found this. But clearly, if we had been working in a university-grant achieving system, there would have been a lot longer time and lag phase in order to have gone ahead and done these studies. We were able to basically get the idea, decide to do them, and do it, and get the results, and at that point then say, "There's something really interesting here. Now we need to see how we're going to afford doing more." But we could do the initial work quickly, because we were able to essentially pursue what seemed like a good scientific idea. It's a great place to work.

Harris: Do you think that a cure and/or a vaccine for AIDS will be developed eventually?

Fox: Sure. Of course. I think it will be difficult, but I actually have no doubt that they will be developed.

Harris: If AIDS had surfaced in 1955, how do you think scientists, the biomedical community, would have reacted?

Fox: I would hope that they would have reacted much as they did, which is to study the problem. However, we wouldn't have had the tools to have found out as quickly as we did what the causes were. This was a class of virus that wasn't even imagined, in fact, went against what everyone's dogma was. So I think that it would have been dealt with, as I suppose I think of another public health scourge, polio or something like that. It would have been studied, it would have been looked at, but I don't think that we would have had, quite the same progress or success. I was just talking about the idea of treating individuals, taking care of individuals, doing research with individuals who have a potentially fatal, transmissible disease. And, really, I think it's just that I was a product of a lucky generation of doctors that didn't really have much to deal with that. But that's something that doctors have always dealt with. Prior to the era of antibiotics, you were always taking care of individuals who could well infect you with something that you could die of. So, in answer to the question, I think that doctors would have responded as they always have, which is that if you have a problem, you try to study it and you try to take care of people. And, of course, there'll always be people who will object to that. But, in general, I think that the profession as a whole has done pretty well and has had a real impact. This has been an exciting time to be here. And certainly one of the things that's always been most exciting about being in NIH in the midst of all this is that you often get to hear about the new discoveries long before you read about them in the *Washington Post*. It's nice to have that opportunity.

Harris: I have heard that someone in NIDR is working on the prospect of developing saliva as a diagnostic tool. Are you involved in that research?

Fox: Oh, yes. That's one of the things that we've been very interested in. There are many ways that saliva can be used in place of blood, for example. In fact, for HIV testing, saliva works very well, and there now is a commercially available test that has the same accuracy and reproducibility as drawing blood. It additionally has some very nice features that it's something that can be completely self-administered, so no one other than the patient has to even touch the sampling stuff. It can be done, collected without any refrigeration and just mailed back in to a central laboratory. So that's just one example, using HIV. There are many, many other things that can be found in saliva that can be used as a surrogate in place of blood. And also, we've been doing some work trying to look for markers for the autoimmune diseases in saliva, looking at a number of different factors, including cytokines and things that might be useful diagnostically for conditions like Sjögren's.

Harris: Well, you mentioned that someone has already developed this as a tool. Was this done at NIDR, or was it supported by NIDR?

Fox: I'm not sure. It wasn't done at NIDR. It certainly built on NIDR-supported research because there was the finding that, as we talked about at the very beginning, that anti-HIV antibodies are present in saliva and in the oral cavity in general, whether they come from serum or from saliva; and that one can utilize saliva as a means of detecting antibodies to the virus. But it was developed, as far as I know, by a private company. Now, whether they had some support in doing that through the SBRI program or something like that, I'm not sure.

Harris: Do you know the name of the company?

Fox: Offhand I don't. I would have to look it up.

Harris: Do you have any papers or records that we might copy for use in history, especially on your AIDS work?

Fox: Oh, sure, yes. I can give you a folder full of them.

Harris: I'll have to come back.

Fox: I can put those together for you and send them to you as well.

Harris: All right. That would be quite useful.

Harden: We may come back around, as I said, with the documents. I will say thank you.

Harris: Thank you ever so much. I think it was a wonderful interview.

Fox: It was delightful talking to you both.

End of Interview